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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,604	07/01/2003	Wei Huang	011068-014-999	4803
20583	7590	03/22/2006	EXAMINER	
JONES DAY 222 EAST 41ST ST NEW YORK, NY 10017			CHEN, STACY BROWN	
			ART UNIT	PAPER NUMBER
			1648	

DATE MAILED: 03/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/612,604	HUANG ET AL.	
	Examiner Stacy B. Chen	Art Unit 1648	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 13 January 2006.
- 2a) This action is **FINAL**.                            2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-19 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 01 July 2003 is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
  1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____.
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
	6) <input type="checkbox"/> Other: _____.

**DETAILED ACTION**

1. Applicant's amendment filed January 13, 2006 is acknowledged and entered. Claims 1-19 remain pending and under examination.

***Claim Rejections - 35 USC § 102***

2. Claims 11 and 12 remain rejected under 35 U.S.C. 102(b) as being anticipated by Nijhuis *et al.* (*Current Opinion in Infectious Diseases*, 2001, 14:23-28, "Nijhuis"). Previously, claims 1-9 were included in this rejection, however, Applicant's amendments to claims 1-9 (removing K103N) renders the rejection of claims 1-9 over Nijhuis moot. Claims 11 and 12 have not been amended in the response filed January 13, 2006.

The claims are drawn to a method for determining whether an HIV-1 has an increased likelihood of having an impaired replication capacity. A virus has an "increased likelihood of having an impaired replication capacity" if the virus has a property, in this case, a mutation, correlated with an impaired replication capacity. The specification (page 10, lines 27-29) states that, "[A] property of a virus is correlated with an impaired replication capacity if a population of viruses having the property has, on average, an impaired replication capacity relative to that of an otherwise similar population of viruses lacking the property. The method steps comprise: detecting whether the reverse transcriptase (RT) encoded by said HIV-1 exhibits the presence or absence of a mutation associated with impaired replication capacity. The mutation occurs at position 98, 100, 101, 103 106, 108, 179, 181, 188, 190, 225 or 236 (not mutation P236L) in said reverse transcriptase. (The reference amino acid sequence for the reverse transcriptase is from HIV NL4-3, Genbank AF324493, see page 12 of the specification.) Specific substitution

mutations are A98G, L100I, K101E, K103N, V106A, V106I, V106M, Y181C, Y188A, Y188C, Y188H, Y188L, G190A, G190C, G190E, G190T, G190V, G190Q, G190S, G190V, P236L and P225H. The mutation confers resistance to a non-nucleoside reverse transcriptase inhibitor, such as nevirapine, delavirdine or efavirenz. Also claimed is a method for determining whether a subject has an HIV-1 with an increased likelihood of having an impaired replication capacity. The subject is undergoing or has undergone prior treatment with an antiviral drug. Also claimed are combinations of mutations that include P236L and K103N.

Nijhuis discloses the implications of antiretroviral resistance on viral fitness. Viral fitness is a synonym for replication capacity (page 23, introduction section). *In-vivo* drug resistance mutations on replication potential for HIV-1 in the presence of non-nucleoside reverse transcriptase inhibitors such as delavirdine include 103N (see Table 1, page 24, and page 25, first column, second full paragraph). Nijhuis teaches that the K103N mutation has a reducing effect on replicative capacity. Nijhuis also discloses that P236L is a NNRTI *in vivo* mutation that reduces replication capacity (Table 1). Given that Nijhuis discloses that the P236L and K103N mutations reduce replicative capacity and is an *in vivo* mutation that occurs after a single dose of NNRTI, the claimed methods are anticipated.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

Applicant argues that Nijhuis does not teach each and every element of claims 11 and 12. In particular, Nijhuis fails to teach the effects of either P236L or the K103N mutation in combination with any other mutation affecting viral replication capacity. Nijhuis does teach the effects on replication capacity of mutation combinations associated with resistance to protease

inhibitors and to nucleoside reverse transcriptase inhibitors, but nowhere does Nijhuis teach, either explicitly or implicitly, the potential effects that the recited combinations of mutations, including combinations comprising mutations in residue 236 or 103, might have on replication capacity. As such Nijhuis does not teach, for example, the effects of mutations at both position 103 and 236 on replication capacity.

In response to Applicant's arguments, it is unclear on what basis Applicant asserts that Nijhuis does not teach the effect of the mutations on replication capacity since Nijhuis teaches that the K103N mutation has a reducing effect on replicative capacity (see Table 1, page 24, and page 25, first column, second full paragraph). Nijhuis also discloses that P236L is a NNRTI *in vivo* mutation that reduces replication capacity (Table 1). Nijhuis discloses that the P236L and K103N mutations reduce replicative capacity and is an *in vivo* mutation that occurs after a single dose of NNRTI. Therefore, the rejection is maintained for reasons of record.

#### ***Claim Rejections - 35 USC § 103***

3. Claims 1-10 and 13-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nijhuis in view of Whitcomb (WO 99/61658). (Previously, claims 1-9 were not included in this rejection. However, Applicant's amendment to claims 1-9 necessitates the rejection of claims 1-9 under 35 U.S.C. 103(a).) The claims are drawn to a method for determining whether an HIV-1 has an increased likelihood of having an impaired replication capacity. The method comprises detecting presence or absence of a mutation associated with impaired replication capacity at at least 2 and up to 12 amino acid positions. Specifically, the combination of mutations is P236L, K103N and Y181C. In some embodiments, the mutation cannot be K103N or P236L. The

teachings of Nijhuis are summarized above. Nijhuis is silent on mutations of more than three positions relating to NNRTIs.

However, Whitcomb discloses means and methods for monitoring non-nucleoside reverse transcriptase inhibitor anti-retroviral therapy, specifically HIV therapy (abstract). Whitcomb discloses substitution mutations in HIV-1 reverse transcriptase at codons 101, 103 and/or 109 that correlate with changes in delavirdine, nevirapine and efavirenz susceptibility (page 12, lines 4-25). Also taught is that mutations at codons 106, 189, 181 and/or 227 of HIV-1 reverse transcriptase result in decreased susceptibility to delavirdine, nevirapine and efavirenz (pages 14-16). Another embodiment of Whitcomb's invention is that a mutation at codon 190 (G190A) either alone or in combination with a mutation at codon 130 (K103N) of HIV-1 RT correlates with resistance to antiretroviral therapy (page 14, lines 29-34). Another embodiment of Whitcomb's invention is that a mutation at codon 236 (P236L) either alone or in combination with mutations at other codons including 103 (K103(N) and/or 181 (Y181C) of HIV RT correlates with resistance to antiretroviral therapy (see description of figures 5 and 6, pages 22-23). Other mutations include 98, 100, 101, 106, 189, 181, 188, 225H and 227 (page 41, lines 13-15).

It would have been obvious to use the mutations taught by Whitcomb in Nijhuis' method. One would have been motivated to incorporate Whitcomb's additional mutations into Nijhuis' method because Nijhuis suggests that there is a relationship between viral replicative capacity and phenotypic resistance (page 27, column 1, second full paragraph). Nijhuis cites several examples including resistance to zidovudine wherein the virus harbors a single amino acid change or a combination of substitutions that have reduced replication capacity compared with

the wild type (Table 1). One would have had a reasonable expectation of success that the detection of other mutations such as those taught by Whitcomb would have been predictive of viral fitness because some of the mutations are the same (K103N, P236L, for example) as those that are associated with both NNRTI resistance and viral fitness. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

Applicant argues that the Office has failed to establish a *prima facie* case of obviousness. Applicant argues that neither Nijhuis or Whitcomb, alone or in combination, teach or suggest that the recited combinations of mutations, including combinations comprising mutations at residue 236 or 103, may correlate with impaired viral replication capacity of an HIV-1 virus having these mutations in its reverse transcriptase. Since the references do not disclose the effects of the recited mutations on replication capacity, the combined disclosure of Nijhuis and Whitcomb fails to teach or suggest either a method for determining whether an HIV-1 has an increased likelihood of having impaired replication capacity or a method for determining whether a subject has HIV-1 with an increased likelihood of having an impaired replication capacity, that comprises detecting a mutation or combination of mutations associated with impaired replication capacity of HIV-1 reverse transcriptase.

In response to Applicant's arguments, it is unclear on what basis Applicant asserts that Nijhuis does not teach the effect of the mutations on replication capacity since Nijhuis teaches that the K103N mutation has a reducing effect on replicative capacity (see Table 1, page 24, and page 25, first column, second full paragraph). Nijhuis also discloses that P236L is a NNRTI *in*

*vivo* mutation that reduces replication capacity (Table 1). Nijhuis discloses that the P236L and K103N mutations reduce replicative capacity and is an *in vivo* mutation that occurs after a single dose of NNRTI. Although Whitcomb does not use the word, “viral fitness”, Whitcomb teaches correlations between various mutations and virus resistance to antiviral therapy, such as mutation at codon 236 (P236L) either alone or in combination with mutations at other codons including 103 (K103 (N) and/or 181 (Y181C) of HIV RT (see description of figures 5 and 6, pages 22-23). Also taught is that mutations at codons 106, 189, 181 and/or 227 of HIV-1 reverse transcriptase result in decreased susceptibility to delavirdine, nevirapine and efavirenz.

Applicant also argues that there is no predictability of whether a mutation associated with resistance will have an effect on replication capacity. Applicant points to Nijhuis, Table 1, as evidence that some mutations or combinations of mutations associated with drug resistance either do not affect or even increase replication capacity. Applicant argues that Whitcomb’s teachings of various mutations associated with NNRTI resistance do not provide a reasonable expectation of success for determining that an HIV-1 is likely to have impaired replication capacity. Applicant argues that impermissible hindsight has led the Office to the claimed invention.

In response to this argument, the combination of Whitcomb’s disclosed mutations and Nijhuis’ suggestion that there is a relationship between viral replicative capacity and phenotypic resistance (page 27, column 1, second full paragraph) is evidence of a reasonable expectation of success that Whitcomb’s observed phenotypic resistance mutations (some of which are the same as Nijhuis’ disclosed mutations, K103N, P236L, for example) will result in reduced replicative

capacity of HIV-1. Note that only a reasonable expectation of success is required, not success itself.

In response to Applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made (Nijhuis' teachings, for example), and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Therefore, the claims are obvious over the Nijhuis in view of Whitcomb.

### ***Conclusion***

4. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

*SPC*

Stacy B. Chen  
March 15, 2006

*James C. Housel*  
JAMES HOUSEL 3/19/06  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600